Rejection Under 35 U.S.C. §112, second paragraph

In the August 5, 1998 Final Office Action, the Examiner rejected claims 15-16, 18-22 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner stated that the recitation of "defect" is vague and indefinite because it is not known what is encompassed by the term. The Examiner stated that for example, "defect" could refer to memory loss, the inability to create a memory, incomplete or incorrect memory building, or other.

During the April 15, 1999 interview, the Examiner reconsidered and agreed to withdraw this ground of rejection. The Examiner indicated that the word "defect" is not indefinite.

Rejection Under 35 U.S.C. §112, second paragraph

In the August 5, 1998 Final Office Action, the Examiner rejected claims 1, 3-6, 15-16, 18-22 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner stated that the recitation of "improving" throughout the claims is vague and indefinite.

During the April 15, 1999 interview, the Examiner reconsidered and agreed to withdraw this ground of rejection. The Examiner indicated that the word "improving" is not indefinite.

Rejection Under 35 U.S.C. §112, first paragraph

In the August 5, 1998 Final Office Action, the Examiner rejected

claims 1, 3-6, 15-16, 18-22 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

During the April 15, 1999 interview, the Examiner reconsidered the rejection under 35 U.S.C. §112, first paragraph. The Examiner took the position that long term facilitation (as studied in *Aplysia*) is not predictive of long term memory in primates. In addition, the Examiner stated that the model described in the specification (i.e., *Aplysia*) is not predictive of recall in primates but is predictive of learning. The Examiner invited applicants to provide evidence and arguments to the contrary.

In response, applicants respectfully traverse the rejection of claims 1, 3-6, 15-16, 18-22 under 35 U.S.C. §112, first paragraph. It is applicants' position that improving long term facilitation as studied in the *Aplysia* gill withdrawal model is predictive of long term memory in mammals. The study of long term facilitation in *Aplysia* is a long-accepted model for the study of long term memory in primates. In support of this position, applicants direct the Examiner's attention to the following references:

Bailey and Kandel (1993) Structural Changes Accompanying Memory Storage. *Ann. Rev. Physiol.* 55:397-426 was submitted as **Exhibit 3** with the Information Disclosure Statement filed October 15, 1996. On page 406 therein, the authors state that the gill and siphon withdrawal reflex of the marine mollusc *Aplysia* can be modified by two forms of nonassociative learning (habituation and sensitization)

each capable of giving rise to <u>a short-term</u>

> memory lasting minutes to hours (citations omitted) and a long-term memory persiting for several weeks (citations omitted).

(Page 406, lines 13-18, emphasis added.) On pages 406-407, the authors describe changes at the cellular and molecular level in *Aplysia* which are characteristics of long-term memory and short-term memory in *Aplysia*.

In addition, Bailey et al. ("Toward a molecular definition of long-term memory storage," *Proc. Natl. Acad. Sci. USA* (1996) 93:13445-13452) (attached hereto as **Exhibit 1**) provide a review of how long-term memory has been more clearly defined via the cellular and molecular mechanisms studied in *Aplysia*. The authors disclose that an implicit form of memory storage in *Aplysia* is a predictive model for memory storage in primates. The authors indicate a "conservation of steps in the mechanisms for learning-related synaptic plasticity." (See abstract.) On page 13445, column 2, the authors state that

> [m]ost striking is the finding that the induction of long-term facilitation at this single synapse in *Aplysia* exhibits a critical time window in its requirement for protein and RNA synthesis characteristic of that necessary for other forms of learning in both vertebrates and invertebrates.

The authors characterize the *Aplysia* model system as a "cellular representation of long-term memory" (see column 1, page 13445, last sentence of first paragraph). Furthermore, the authors provide experimental results obtained with the *Aplysia* model and comment that

> these results suggest that *Aplysia* C/EBP, an immediate-early gene activated during the consolidation phase of long-term faciliation, serves as part of a molecular switch for

converting short-term memory to long-term memory.

See page 13449, column 2, lines 6-10. In addition, on page 13451, the authors point out the similarity between the mammalian memory system and the *Aplysia* system. The authors first ask "is there a similar set of molecular steps for memory consolidation .... in the mammalian brain?" Then, the authors provide evidence showing the similarity and state "similar to the presynaptic facilitation in *Aplysia*, both mossy fiber and Schaffer collateral LTP have distinct temporal phases, each with a cellular representation." See column 2, page 13451, 2nd paragraph and 4th paragraph. The authors also state that "thus, as in *Aplysia* presynaptic facilitation, cAMP-mediated transcription appears to be a common mechanism for the late form of LTP in all three pathways within the hippocampus (Fig. 6)." See last 5 lines of column 2 of page 13451.

Finally, the authors summarize their findings on page 13452 (see column 1, "An Overall View"). Bailey et al. draw a direct correlation between the molecular steps identified in the *Aplysia* system and studies performed in the hippocampus of the vertebrate brain. Bailey et al. note "the apparent similarity in some of the molecular steps that underlie learning-related synaptic plasticity..." Applicants urge that there have been numerous studies which show that that cellular and molecular mechanisms which underlie the long-term facilitation in *Aplysia* correlate to and are predictive of the development of long-term memory in mammals.

Kandel provides a further description of this correlation in "Genes, Synapses, and Long-term Memory" (1997) *J. of Cellular Physiology* 173:124-125 (attached hereto as **Exhibit 2**). Kandel

asks to what degree implicit learning and explicit learning share common molecular steps (see last sentence, first paragraph of column 1, page 124). Kandel states that studies on *Aplysia* gill withdrawal reflex, a form of implicit learning, "have revealed a representation of short- and long-term memory at the cellular level." (See 11 lines up from bottom of column 1, page 124). Kandel further states that "mechanisms for the late phase of LTP, thought to be important for long-term memory storage following explicit forms of learning, resemble those utilized in *Aplysia* and in *Drosophila* for storing behavioral long-term memory for implicit tasks." See column 2, page 125, lines 11-15. Kandel concludes that the mechanisms used for storage of long-term memory may be conserved (see last sentence of reference). Therefore, the *Aplysia* model would be predictive of the long-term memory storage in primates.

Based upon the foregoing evidence, applicants submit that the *Aplysia* gill withdrawal model is predictive of the molecular and cellular mechanisms of primates. Thus, applicants maintain that the subject specification is fully enabling for the presently claimed ivention. Applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

<u>Rejection Under 35 U.S.C. §102</u>

The Examiner rejected claims 1, 3-5, and 18-21 under 35 U.S.C. §102(a or b) as being anticipated by Yin et al. (1994).

During the April 15, 1999 interview, the Examiner indicated that if applicants can provide evidence that the dCREB2a and dCREB2b

referred to in the Yin et al. (1994) reference is a CREB1, then the Examiner would consider withdrawing the rejection.

In response, applicants maintain that Yin et al. do not anticipate the presently claimed invention. Applicants submit that the dCREB2a and dCREB2b referred to in Yin et al. (1994) are actually isoforms of CREB1.

Applicants submit herewith Yin et al. (1995) "A Drosophia CREB/CREM Homolog Encodes Multiple Isoforms, Including a Cyclic AMP-Dependent Protein Kinase-Responsive Transcriptional Activator and Antagonist" *Molecular and Cellular Biology* 15(9):5123-5130 (attached hereto as **Exhibit 3**). Figure 4 of this reference indicates that dCREB2a is homologous to the mammalian CREB1 sequence (and to CREM and ATF-1). Incidentially, CREB1 was later cloned by Bartsch et al. (see **Exhibit 4** hereto, Bartsch et al. "CREB1 encodes a nuclear activator, a repressor, and a cytoplasmic modulator that forms a regulatory unit critical for long-term faciliation" Cell 95:211-223). The sequence comparison of dCREB2a and dCREB2b indicate that these are isoforms of CREB1 and not CREB2.

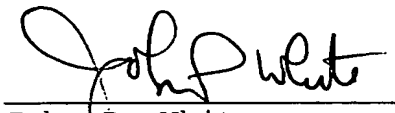
Applicants urge that the dCREB2a and dCREB2b are not the "cAMP-responsive-element-binding-protein-2" as presently claimed. Applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Reconsideration and allowance of the present application in view of the foregoing amendments and accompanying remarks is respectfully requested.

If the Examiner has any questions regarding this Communication she is cordially invited to telephone the undersigned attorney.

No fee, other than the CPA filing fee and the extension of time fee, is deemed necessary in connection with the filing of this Preliminary Amendment. If any additional fee is necessary, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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